CERTIFICATE OF MAILING
I HEREBY CERTIFY
THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST-CLASS MAIL IN AN ENVELOPE ADDRESSED TO: COMMISSIONER OF PATENTS AND TRADEMARKS, WASHINGTON, D.C. 20231, ON 25 September 1996

Mary E. McCabe
AGENT/ATTORNEY FOR APPLICANT

25 September 1996
DATE

Attorney Docket No. P50317

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Lukas-Laskey, et al.	September 25, 1996
Serial No.:	08/483,635	Group Art Unit No.: 1205
Filed:	June 7, 1995	Examiner: W. Jarvis
For:	METHOD OF TREATMENT FOR DECREASING MORTALITY RESULTING FROM CONGESTIVE HEART FAILURE	

DECLARATION OF NEIL H. SHUSTERMAN, M.D.

I, NEIL H. SHUSTERMAN, M.D., a citizen of the United States of America, do hereby declare:

1. THAT, I obtained my medical degree in 1978 from Jefferson Medical Center, and that since 1989 I have been employed by SmithKline Beecham Corporation, operating as SmithKline Beecham Pharmaceuticals;

2. THAT, I am presently employed in the capacity of Vice President and Director of the Cardiovascular Therapeutic Unit of Clinical Research, Development and Medical Affairs in Research and Development of SmithKline Beecham Pharmaceuticals, and that I am responsible for the clinical development of carvedilol;

3. THAT, I am a joint inventor in the above-identified patent application and that I am familiar with said application;

4. THAT, the following clinical studies were performed under my direction:

- study 220, a dose response study in moderate (NYHA II-IV) CHF with exercise testing as a primary endpoint
- study 221, a dose titration study in moderate (NYHA II-IV) CHF with exercise testing as a primary endpoint
- study 239, a dose titration study in severe (NYHA III-IV) CHF with quality of life as a primary endpoint
- study 240, a dose titration study in mild (NYHA II-III) CHF with progression of CHF as a primary endpoint

with sixty-four centers in the US participating in the trial program;

5. THAT, the following table summarizes the reduction in mortality for carvedilol-treated CHF patients in the above-noted clinical trials:

	Carvedilol	Placebo	Risk Reduction (95% CI)	p value*
All Cause Mortality	18/624 (2.9%)	29/356 (8.2%)	67% (42-81)	<0.0001
Class II CHF	7/361 (1.9%)	12/202 (5.9%)	68% (20-97)	0.015
Class III-IV CHF	11/263 (4.2%)	17/154 (11.0%)	66% (30-84)	0.004
Ischemic Etiology	10/311 (3.2%)	16/178 (8.9%)	67% (32-85)	0.003
Non-Ischemic Etiology	8/313 (2.5%)	13/178 (7.3%)	67% (20-86)	0.014

* Cochran-Mantel-Haensel Analysis;

6. THAT, this data demonstrates that carvedilol reduces mortality by about 67% in all-cause mortality;

7. THAT, in my opinion, this reduction in all-cause mortality in CHF patients treated with carvedilol is unexpected and significant, since known β-adrenoceptor antagonists had no statistically significant effect on all-cause mortality, as summarized in the table below:

Reference	**Antagonist**	**Observation**
Waagstein, et al., *Lancet*, 342:1441-1446 (1993) at 1445	metoprolol	no effect on all-cause mortality
CIBIS, *Circulation*, 90:1765-1773 (1994) at 1771	bisoprolol	failed to demonstrate overall reduction in mortality

8. THAT, in my opinion, the discovery that carvedilol reduced mortality by about 67% in CHF patients satisfies a long-felt need which was recognized, but not solved, by others, as evidenced by the fact that standard agents for treating CHF, such as diuretics, digitalis glycosides, vasodilators (excluding ACE inhibitors), and ionotropic agents, relieve the symptoms of the disease, but are not known to reduce the mortality rate in CHF patients, and that even though ACE inhibitors reduce mortality in CHF patients, this reduction is only on the order of 20%;

9. THAT, in my opinion, one of ordinary skill in the art of medicine reading the data and results presented hereinabove would conclude that carvedilol exhibits a surprisingly and unexpectedly superior property when compared to other agents for treating CHF, and thus that carvedilol provides superior treatment for congestive heart failure, when compared to known agents, since it reduces mortality in CHF patients by about 67%.

10. THAT, I further declare that all the statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States

Serial No.: 08/483,635
Group Art Unit No.: 1205

Code, and that such willful false statements may jeopardize the validity of the present application or of any patent issuing thereon.

Neil H. Shusterman, M.D.

25 Sep 96

Date

n:\nem\ptolrs\aff50317.doc